

The final study (51) again used 20 young medical persons divided among 10 smokers and 10 nonsmokers. The mean pulmonary compliance was significantly greater for the nonsmokers than for the smokers.

Since cigarette smokers have a chronically elevated carboxyhemoglobin level, usually greater than 2 percent and occasionally exceeding 10 percent, a study (19) was performed having nonsmokers inhale enough carbon monoxide to raise their carboxyhemoglobin levels to the range seen in a control group of cigarette smokers. This maneuver caused the development, in the study group of nonsmokers, of an increased oxygen debt with exercise and a reduced pulmonary diffusing capacity at rest. These changes after carbon monoxide inhalation were similar to those found without carbon monoxide inhalation when comparing cigarette smokers to nonsmokers. (Further data concerning smoking and carbon monoxide is presented and discussed in the chapter on cardiovascular diseases in this report.)

### RÉSUMÉ

Findings from various studies relating smoking to pulmonary function are less consistent for certain criteria of measurement than from those relating smoking to respiratory symptoms. They are, however, consistent in that they all report some form of diminished pulmonary function among cigarette smokers, even when relatively young smokers were studied. This is true of the studies outlined here as well as others that have not been included (18, 40, 56, 58, 81). The usual measurement found to be lower among smokers is the 1-second forced expiratory volume ( $FEV_{1.0}$ ) either alone or as a ratio of the vital capacity ( $FEV_{1.0}/VC$ ). Vital capacity alone was generally not found to be associated with smoking but diminished flow rates, such as  $FR_{75}$ ,  $FR_{50}$  and the peak expiratory flow (PEF), were often observed. In these studies, distinct quantitative relationships were not observed between impairment of pulmonary function and the number of cigarettes smoked daily.

### RELATION OF SMOKING TO HEREDITY OR TO CONSTITUTIONAL FACTORS

Although various surveys and studies consistently show an association between smoking and respiratory symptoms and mortality from respiratory disease, there have been objections to interpreting this relation as causal. Arguments have been made that smokers and nonsmokers may differ in some respects, perhaps biological, that are relevant to the occurrence of disease. Others have suggested that pre-

dispositions to smoking and respiratory disease may have a common genetic basis.

One method of trying to estimate the importance of heredity and constitutional factors is to study the effect of tobacco smoking among pairs of twins, particularly identical (monozygotic) twins. If, when one twin in each pair of monozygotic and dizygotic twins is a smoker and the other is not, an excess morbidity does *not* appear among the smoking twins, it would seem that the exposure to tobacco smoke was insufficient to result in greater morbidity. Cederlof and his associates (16, 17) in Sweden studied smoking in relation to morbidity from various causes among 12,889 pairs of twins. Replies to a mailed questionnaire dealing with smoking habits and residential history were received from 10,947 pairs (85 percent). Replies to a second questionnaire with medical questions were received from both members of 9,319 pairs—another response of about 85 percent.

A subject who answered "Yes" to the question, "Do you regularly have a cough?" was regarded as having "cough." If, when asked, "For how many consecutive months a year do you have a cough?", the subject checked more than 3 months, he was regarded as having "bronchitis."

If the group comprising only one of each twin pair (the first twin on the twin registry) is considered as a random population, the association observed between smoking and respiratory symptoms is given in table 11.

TABLE 11.—*Prevalence of "cough" and "bronchitis" among smokers and nonsmokers by sex and age*

Sex and birth year	Cough		Bronchitis	
	Smoker	Nonsmoker	Smoker	Nonsmoker
Men:				
1886-95.....	17.7	17.8	7.4	5.5
1896-1905.....	15.5	6.6	6.7	2.5
1906-15.....	15.0	5.5	6.3	1.6
1916-25.....	13.8	3.5	4.9	1.2
Women:				
1886-95.....	25.0	8.7	8.3	2.7
1896-1905.....	18.0	7.0	8.0	2.4
1906-15.....	14.2	5.5	4.8	1.4
1916-25.....	11.1	3.8	2.9	.6

SOURCE: Cederlof, R., et al. (17).

These findings are similar to those previously reported for various populations. These respiratory symptoms were then analyzed among twin pairs with discordant smoking habits, that is, one twin of the

pair never smoked and the other either had smoked or still smoked at the time of the survey. The findings are presented in table 12.

TABLE 12.—*Prevalence of "cough" and "bronchitis" among smokers and nonsmokers in smoking-discordant twin pairs*

Twins	Cough		Bronchitis		Number of pairs
	Smoker	Nonsmoker	Smoker	Nonsmoker	
Monozygotic:					
Men.....	14.6	7.7	6.6	1.1	274
Women.....	13.6	7.6	3.0	2.3	264
Dizygotic:					
Men.....	12.3	5.5	4.5	1.8	733
Women.....	14.5	5.7	5.5	1.8	653

SOURCE: Cederlof, R., et al. (17).

This table shows that the prevalence of respiratory symptoms was much higher among the smokers in twin pairs than the nonsmokers. The authors concluded that this hypermorbidity "speaks in favor of a causal interpretation."

In a further analysis of the data from monozygotic twin pairs with discordant smoking habits, Cederlof and his coworkers (15) divided the series into a "low risk group" in which the nonsmoking twin did not have "cough," and a "high risk group" in which the nonsmoking twin had "cough." The two groups of smoking co-twins corresponding to the two nonsmoking risk groups had higher than expected prevalence rates. The observed value for smokers in the low risk group, however, was only half that expected for nonsmokers in the high risk group. This suggests that for some *individuals* the genetic influence may be more important than smoking in the development of cough. But, because any high risk group is only a small part of the population, the total genetic effect will be much smaller than the effect of tobacco.

Lundman (53) made a detailed study of twin pairs in Sweden. Of 247 twin pairs asked to participate, 196 pairs were examined (80 percent), of which 92 were monozygotic and 104 dizygotic. All participants were interviewed and examined without knowledge of their smoking habits. All twin pairs were concordant with respect to urban/rural residence and discordant in smoking habits. After estimation of lifetime exposure to smoking, 30 pairs were considered concordant, thus limiting analysis to 77 monozygotic and 89 dizygotic pairs. The smokers in both groups of twins had significantly higher frequencies of some respiratory symptoms, such as persistent cough and morning phlegm, but not of other symptoms such as dyspnea, "day cough", and "day phlegm". Smokers also had "an increase in the unevenness of

ventilation measured by nitrogen washout, and an increase in airway resistance as measured by dynamic spirometry."

#### RÉSUMÉ

Two recent studies (17, 53) of populations of identical and fraternal twins show that for some individuals in the populations studied a genetic element appears to be of some importance for the development of cough. However, the effect of smoking was clearly shown to be much more important for most of the individuals in the total populations studied. One study (53) also clearly showed that smoking twins more often had reduced ventilatory function tests as compared to their respective nonsmoking twins.

These data provide strong confirmatory evidence that cigarette smoking can cause chronic bronchitis; however, no inferences with respect to pulmonary emphysema can be based on these data. Studies such as these, when specifically designed to provide additional information about pulmonary function, may be helpful in evaluating the relationship between cigarette smoking and pulmonary emphysema.

#### PATHOLOGY STUDIES

Very few papers relating the gross and microscopic appearance of the trachea, bronchi, and lung parenchyma to tobacco smoking have appeared in the last 3 years. Auerbach and his coworkers have continued their analysis of bronchial tissues taken from 758 subjects (7) and lung parenchymal tissue taken from 1,340 men (8). They published a report (9) correlating findings in the bronchial tree with findings in the lung parenchyma of 267 men who were included in both previous studies. They reported a high correlation between fibrosis in the lung parenchyma and different abnormalities of the bronchial epithelium, such as hyperactive glands, increased number of cell rows in the ciliated epithelium, and increased frequency of cells with atypical nuclei. As reported previously by and summarized in the Surgeon General's 1964 Report, more frequent and more severe abnormalities were observed among cigarette smokers. Sections of the bronchial tree among ex-smokers were more like those of nonsmokers while fibrotic changes in the lung parenchyma were more like those observed among smokers.

Changes in the bronchial tree similar to those described by Auerbach and his coworkers were reported in a series of 100 random adult autopsies by Hernandez and Anderson and their associates (38). They reported a higher frequency of abnormal epithelial hyperplasia, goblet cell hyperplasia, round cell infiltration, congestion, and edema in

bronchi from smokers than nonsmokers. There was, however, no evidence of more bronchial gland hyperplasia.

These same workers also studied macroscopic sections of single lungs from 211 routine autopsies on adults (1, 2). Analysis was limited to 165 of these cases on whom smoking histories were obtained, usually from relatives. Without knowing the identity of the subject or his smoking history, each lung section was classified on a scale from 0 to 6 by severity of emphysematous changes. The type of emphysema was also described as panlobular (changes throughout the secondary pulmonary lobules), centrilobular (changes located around the centers of the secondary lobules), or mixed. The severity of emphysematous changes was about the same for men and women, but for each sex, changes were more severe among smokers than nonsmokers, as seen in table 13.

TABLE 13.—*Mean severity of emphysema classified by macrosections by sex and smoking history*

	Number	Mean degree of emphysema		Number	Mean degree of emphysema
Men:			Women:		
Smokers.....	96	2.3	Smokers.....	18	2.1
Nonsmokers....	11	1.1	Nonsmokers....	40	.8

SOURCE: Anderson, A. E., Jr., et al. (8).

Perhaps more important was the observation that the type of pathology seemed strongly related to smoking (2). Of 48 subjects whose lung macrosections were classified as having mainly centrilobular emphysema, 45 persons had been smokers. In contrast, the 62 subjects judged to have panlobular emphysema were divided in the expected proportions, 38 smokers and 24 nonsmokers.

Petty and his associates (61) also studied postmortem findings in the lungs of a series of 253 men over age 40, unselected for smoking, who died in two Denver hospitals during a 6-year period from 1959 to 1965. The presence and severity of emphysema was estimated and graded in four categories, from 0 to 3+. During the last 3 years of the study bronchi of 179 men were examined for mucous gland hyperplasia. Independent of the morphological studies, smoking histories were obtained for each person, apparently by questioning relatives, although this is not clearly stated. Men were grouped according to the amount of cigarettes smoked during their lifetimes by calculating pack-years of smoking. (One pack-year is the number of cigarettes smoked if a person smoked one pack per day for a year. A pack-year could also mean smoking two packs a day for 6 months, one-half pack a day for 2 years, or any equivalent amount.)

Of the group of 179 individuals, 54 had mucous gland hyperplasia. Of the 54 persons involved, 51 had smoked more than 20 pack-years, and the remaining three were essentially nonsmokers. In contrast, approximately one-third of the 125 men in whom mucous gland hyperplasia was not found were essentially nonsmokers. When the total group of 253 men was studied for evidence of pulmonary emphysema, 114 were found to have moderate or severe pulmonary emphysema. Of the 114, 98 had smoked more than 20 pack-years. The other six, who essentially were nonsmokers, had either asthma, previous tuberculosis, deep-seated lung infections or other demonstrable relationships with previous pulmonary disease. In contrast, approximately one-third of the remaining 139 men, who had either very mild or no emphysema, were essentially nonsmokers.

Only one study has been found in which the frequency of abnormal bronchial epithelial cells in living persons is compared with smoking history. Robbins (63) studied a group of 103 college students between the ages of 17 and 24. Of the 45 who had never smoked, atypical epithelial cells were found in six (13 percent). This compares to 26 (45 percent) of the 58 students who had been smoking 10 or more cigarettes daily for 1 to 8 years. Cytological examination was done without knowledge of whether the specimen came from a smoker or nonsmoker.

## ANIMAL EXPERIMENTS

Results of two experimental studies relating smoke inhalation to lung parenchymal changes in dogs have been published in the last 3 years. Hernandez and his coworkers (39) used 23 healthy greyhounds retired from racing. Eight served as controls and 15 were exposed to high concentrations of cigarette smoke for 30–45 minutes twice daily in wooden inhalation chambers. Seven animals were exposed for approximately 5 months and the remaining eight were sacrificed after almost 15 months of smoke inhalation. Disruption of the lung parenchyma was assessed macroscopically by comparison with preselected standards graded in severity from 0 to 3. Assessment was made without knowledge of the source of the lung specimen. Lung damage among dogs that were exposed longer showed significantly greater disruption of the lung parenchyma.

Auerbach and his associates (5, 6) tracheostomized 10 adult beagles and, in an attempt to approximate human smoking more closely, exposed them to cigarette smoke through the tracheostomy tube. Five dogs died during this experiment and the remaining five were sacrificed after approximately 14 months of exposure. Other beagles

were kept as controls; two had tracheostomy openings. These control dogs were sacrificed at the time the last five smoking dogs were sacrificed. Lungs of the dogs exposed to cigarette smoke showed microscopically the presence of dilated air spaces, especially beneath the pleural surface. Here the alveolar septa showed a fibrous thickening of the walls with areas of rupture and dilated air sacs. Padlike attachments to alveolar septa were found. These zones of connective tissue surrounding dilated air sacs were also visible macroscopically as white areas on the lung surface. There was no thickening of the walls of small arteries and arterioles within the lung. The lungs of the control dogs were normal in appearance with none of these changes. These abnormalities approximate but are not fully concordant with some of the typical pathological findings in human emphysema. This experiment does indicate that inhaled cigarette smoke apparently can damage the pulmonary parenchyma of dogs. Other findings (6) as yet unpublished, indicate that abnormalities of the bronchial epithelium resulted that approximate many of the histopathologic findings of human chronic bronchitis.

Rockey et al. (64) have noted that cigarette smoke produces bronchial and parenchymal changes in dogs that approximate some of the histopathologic findings found in human smokers who have chronic bronchitis and/or pulmonary emphysema. Mouzakis (57) has noted similar changes in rabbits, and in dogs exposed to cigarette smoke through tracheostomies.

#### RÉSUMÉ

Researchers carrying out pathological studies have consistently reported epithelial hyperplasia of the bronchial tree associated with smoking. They have also reported that fibrosis and emphysematous changes in the lung parenchyma, although observed among non-smokers, occur much more frequently among men and women who have histories of smoking. Changes in the lung parenchyma, approximating some of the changes noted in human emphysema, have also been produced experimentally in dogs by exposure to cigarette smoke.

#### CILIATOXIC EFFECTS OF CIGARETTE SMOKE

The toxic effect of tobacco smoke on the ciliary defense mechanism of the respiratory system has been confirmed by additional experimental studies (9, 10, 13, 23, 24, 26, 27, 45, 47, 77, 78) which seek to determine more exactly the mode of action of the ciliatotoxic agents contained in tobacco smoke. As yet, hydrogen cyanide and acrolein appear to have the greatest ciliatotoxic effects of the agents that have been identified in the gaseous phase of tobacco smoke, although for-

maldehyde, crotonaldehyde, formic acid, acetic acid, propionic acid, and some phenols are also ciliotoxic (25, 46, 48, 73, 77, 79). Further information may be obtained from a special symposium on ciliary activity held in 1965 (48). A recent study (22) suggests that oxidative enzymes such as adenosine triphosphatase, apparently important to ciliary activity, may be adversely affected by cigarette smoke. Additional research is necessary before precise conclusions can be stated concerning which, if any, of the identified ciliotoxic agents contained in tobacco smoke are most damaging to the human respiratory system.

#### OTHER FACTORS ASSOCIATED WITH CHRONIC BRONCHITIS OR EMPHYSEMA OR BOTH

It is not the purpose of this report to discuss all the factors that may play a role in the development of chronic bronchitis and emphysema. It is important, however, to recognize that these conditions do exist among people who do not smoke and that many smokers apparently escape all signs of affliction. It is also important to recognize that other factors have been associated with the development of chronic respiratory disease, or chronic bronchitis and emphysema, as we have defined chronic respiratory disease. We must be concerned with the multiple etiology of biological processes. One factor already cited is the role of hereditary or constitutional factors in the development of respiratory symptoms, either operating alone or in conjunction with other factors such as smoking.

Aside from the personal pulmonary pollution inherent in smoking, occupational exposures (a wider form of pollution) and exposure to various pollutants in the atmosphere have both been shown to influence the prevalence of respiratory signs and symptoms. Studies made in some specific industries—for example, pulp mill workers in New England (32), coal miners in West Virginia (31), and gold miners in South Africa (66, 67)—have shown an increased frequency of respiratory symptoms or of diminished pulmonary function among men exposed to certain dusts and fumes.

These studies indicate that cigarette smoking is generally more important than the occupational exposures in producing respiratory disease in the workers. These studies also suggest that cigarette smoking may interact with some occupational exposures to produce even greater deleterious effects. Cigarette smokers outnumber by far the workers subjected to unusual environmental exposures. Also, there has been a general improvement in many occupational environments, in the continuing effort to remove or reduce the exposure to specific industrial air pollutants.

Climatic and meteorologic variations involved with differences in quantity and quality of specific air pollutants make investigations of atmospheric pollution very complex. There have been many studies, however, attempting to examine the association of air pollution with chronic respiratory disease. Often comparisons of mortality and morbidity are made between urban and rural areas, assuming a difference in air pollution but not measuring it directly. Wicken (75) in his retrospective study of mortality from chronic bronchitis in Northern Ireland found higher mortality rates with greater degrees of urbanization. Air pollution was suggested as a factor.

Holland and Reid (42) compared the prevalence of respiratory symptoms, sputum production, and lung function in London and in three county towns. The London men had more and severer symptoms, produced more sputum and had poorer lung function test results. Smoking habits were shown to be closely related to respiratory disturbance but urban-rural differences in these habits could not explain the greater frequency of respiratory symptoms in London.

A Canadian study reported by Bates et al. (11) indicates that among four cities studied, the city with the lowest amount of industrial dust-fall and sulfur dioxide levels had the study group with the lowest prevalence of chronic bronchitis. Preliminary results also indicate that this group had the lowest decline of pulmonary function. The groups of males in each city were approximately concordant for other factors, including the influence of cigarette smoking.

Ferris and associates (3, 4, 33) studied air pollution and its effect on respiratory symptoms and functions in two separate towns—Chilliwack, British Columbia, and Berlin, N.H. After standardizing the data for age and cigarette smoking, they observed a correlation between symptoms of chronic bronchitis and the level of air pollution as measured by the mean sulfation rate. They also found pulmonary function tests to be better in Chilliwack when controlled for smoking habits and age. This may be associated with the lower level of air pollution in Chilliwack.

Studies of populations of twins are especially valuable in assessing the influences of constitutional factors and environmental considerations, such as cigarette smoking and air pollution. Cederlof (14), using interview techniques on a large population of twins in Sweden, found that compared with smoking, air pollution was of secondary importance in causing respiratory symptoms indicative of chronic bronchitis and/or emphysema. In both the monozygotic and dizygotic twins, again using the co-twin control method, individual variations suggested that the propensity to develop cough from smoking also may well be pertinent with regard to air pollution but that, when considering the total population, individual variations appear to be of minor influence (15).

Other studies (55, 76) have suggested a relation between air pollution and symptoms or mortality from chronic respiratory disease, although they were not controlled for differences in cigarette smoking.

The contributions of air pollution, industrial pollution, and personal pollution have been summarized recently by Higgins (40). He concluded, as we must from the available evidence, that all "\* \* \* three types of pollution are associated with increased amounts of respiratory disease and respiratory disability." All the recent evidence, however, does not alter the conclusion in the Surgeon General's 1964 Report that "the dominant association in the United States is between cigarette smoking and chronic respiratory disease."

#### ADDITIONAL CONSIDERATIONS REGARDING SMOKING AND EMPHYSEMA

This crucial question must be answered affirmatively before an inference can be made that smoking directly causes pulmonary emphysema: Does inhaled tobacco smoke have a direct toxic effect on the alveolar tissue in the lung parenchyma which is important in the pathogenesis of pulmonary emphysema? At present, it cannot be answered.

If future evidence supports such a finding of a direct toxic effect, we will have the missing link to the present chain of evidence showing a strong association between cigarette smoking and many cases of pulmonary emphysema and an inference of causation may validly be made. The available evidence that follows has only indirect pertinence to the question.

The experiments of the Auerbach, Hernandez, and Rockey groups support the thesis that there is a direct toxic effect of cigarette smoke on the pulmonary tissue. Possibly this direct toxic effect, if proven to exist, contributes to the rupture and fibrosis of the alveolar tissue. However, in these animal studies there were also some differences from the typical anatomic findings of human pulmonary emphysema.

Surfactant, a fluid substance lining the alveolar cell walls, apparently is important for maintaining tissue surface tension and thus the spatial configuration of the alveolar walls (65). *In vitro* abnormalities have been noted in surfactant as a result of cigarette smoke (21, 74). Alveolar macrophages (specialized cells that incorporate and remove foreign material from the affected lung area) are reportedly damaged *in vitro* by cigarette smoke (35). Abnormalities of the alveolar macrophages and lipophages with inhalation of cigarette smoke are also reported (54) in cytological studies of human bronchial washings, apparently reflecting damage *in vivo*.

Studies (49, 50, 51, 62) of the pulmonary function of relatively young smokers and nonsmokers also indicate that abnormalities of pulmonary diffusion noted in cigarette smokers, may, in part, be related to a direct toxic effect of cigarette smoke. However, some of these abnormalities are related to the unevenness of pulmonary ventilation associated

with airway abnormalities. Damage to the pulmonary arterial capillaries has frequently been noted on autopsy examination of smokers. This damage may be a direct effect of smoke inhalation and, functionally, may impair the vascular perfusion of the alveolar tissue, thus leading to further deficiencies in alveolar tissue function.

The possibility must also be considered that the accelerated *in vitro* thrombus formation (discussed in the cardiovascular chapter of this report), associated with cigarette smoking, may be the basis for multiple small thromboses in the pulmonary arterial capillaries.

Additional research is also needed to answer questions concerning other factors that may account for the apparent increased susceptibility of some individuals to cigarette smoke, such that they have a marked excess mortality from this disease. Genetic and constitutional factors may be important to some individuals' development of pulmonary emphysema, just as these factors appear to be important in the development of cough in smokers, as reported by Cederlof and his associates (14, 15, 16, 17). An increased susceptibility of some individuals to the emphysema associated with cigarette smoking has been suggested, but not proved, by the occasional reports of "familial" emphysema (41, 52).

Other probable causes of pulmonary emphysema, such as allergic or infectious disease processes, also should be investigated for interactions with and without smoking. Other apparent causes of pulmonary emphysema, such as possibly atmospheric air pollution, may be interacting with cigarette smoking to produce effects even more deleterious to human health.

The observation that other probable causes of pulmonary emphysema may exist should not detract from the strong relationship that has been shown to exist between cigarette smoking and pulmonary emphysema. Further investigations of the mechanisms of injury to the cellular and subcellular structures of the lung tissue are recommended (34). Also, clarification of diagnostic nomenclature and criteria would be helpful, as indicated in the earlier discussion of definitions in this chapter.

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## CHAPTER 3

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### Smoking and Cancer

#### CONTENTS

	Page
General Chemical and Experimental Data on Carcinogenesis and Tobacco Smoke.....	127
<i>In Vitro</i> Cellular Changes by Tobacco Smoke.....	129
<i>In Vivo</i> Tumor Formation by Tobacco Smoke.....	129
Tumor-Promoting Agents in Tobacco Products.....	130
Lung Cancer.....	131
Mortality Data.....	131
Histopathology of Lung Tumors.....	140
Experimental Pulmonary Carcinogenesis.....	144
Additional Evidence Concerning Experimental Carcinogenesis.....	144
Cancer of the Buccal Cavity and Pharynx (Lip, Mouth, Throat).....	145
Cancer of the Larynx.....	148
Cancer of the Esophagus.....	149
Cancer of the Urinary Bladder.....	153
Cancer of the Stomach.....	157
Cancer of the Pancreas.....	158
Cited References.....	161
Supplemental References.....	167